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APPLICATION OF THE REMOTE PHOTOCYCLIZATION WITH A PAIR SYSTEM OF PHTHALIMIDE AND METHYLTHIO GROUPS

A PHOTOCHEMICAL SYNTHESIS OF MACROLIDE MODELS[1]

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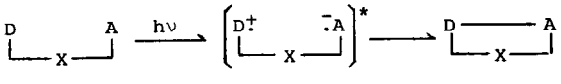
Abstract—Based on the regioselective remote photocyclization of a pair system consisting of a phthalimide group and a terminal sulfide group in their side chain, a variety of azathiacyclic compounds containing 9- to 27-membered rings were synthesized.

The importance of macrocyclic compounds in biological and chemical systems has recently attracted considerable attention. Large number of macrocyclic natural products including antibiotics such as depsipeptides and macrolides have been isolated, and in many cases their roles as ligands in complexing various metals have been identified.[2] Typically, crown ethers and cryptands are well known examples of synthetic macrocyclic ligands.[3] Although many ground-state reactions for the construction of macrocycles have been known,[4] much less information is available for photochemical macrocyclic syntheses.[4]

During the course of our systematic studies on the imide photochemistry,[5] we have found that N-substituted phthalimides (=1,3(2H)-dioxo-2H-isoindoles) possessing a terminal sulfide function in their side chain undergo unusually facile photocyclization to give azathiacyclols.[6] We are extending this type of reaction to general synthesis of macrocycles on the basis of a regioselective remote photocyclization of a "pair system" which consists of, in this case, a phthalimide group and a methylthio group. With this particular pair, macrocycles of up to 16-membered,[7] cyclic peptide models of up to 21-membered[8] and crown ether analogs of up to 15-membered,[9] have been synthesized. While the phthalimide ring is a good electron acceptor (A), the sulfide is a donor (D). Therefore it is assumed that a complex formation in the excited states may facilitate the reaction, suggesting a general working hypothesis that compounds possessing appropriate D–A pair groups, even separated by a long chain, are capable of forming a new C–C bond on irradiation (Chart 1).



1 X=**a**: [–CONH–] **b**: [–O–] **c**: [–CO_2–]

Chart 1.

In photoprocesses the reactivities often seem to be more sensitive to the structural and the environmental factors than in thermal processes.[10] Therefore, in order to see the scope and limitation of the above synthetic approach, careful examination of a structural variation in the connecting part (X), which combines the donor and the acceptor, was needed (Chart 1). We have already investigated the photocyclization of the phthalimides containing amide[5–8] and ether[9] bonds in their long side chain (**1a–b**). In addition, we have preliminarily reported the results of the photochemical synthesis of macrolide derivatives of such a pair system with an ester bond in their side chain as a connecting part (**1c**).[11] In the present paper we wish to report a full account of this photochemical synthesis of macrolide models.

A series of phthalimides **6** and **8**, possessing a ω-terminal sulfide function in their ester bond side chain in the alcohol and the acyl portion, respectively were prepared by the reactions shown in Chart 2.

A solution of substrate **6** (or **8**) in acetone (3–7 mM) was irradiated with a 400 W high -pressure mercury lamp in a stream of argon for 30–110 min. As shown in Table 1, in most cases a mixture of **9** (or **12**) and **10** (or **13**) were obtained, with the former as a major product, after silica gel column chromatography in moderate yields (35–80%). The assignment of these structures was made on the basis of elemental analyses and their spectral properties. For example, in the ^{1}NMR spectrum of **9a**, a medium-sized compound obtained from **6a**, appeared a new peak of a methylene moiety at δ 2.98 and 3.56 as an ABq-type (J = 14.8 Hz), in place of the original S-Me group in **6a**, and a peak of an OH group appeared at δ 3.57–4.00, in support of the cyclol moiety. The IR signals of an OH and CO groups in **9a** appeared at ν 3380 cm^{-1} (OH) and 1740, 1695 and 1685 cm^{-1} (CO's), respectively. All other spectral and analytical data satisfied the structure **9a**. The cyclol **9a** was readily converted into the dehydrated product **11a** [NMR; δ 6.42 (1H, s, olefinic proton)] through the treatment with *p*-toluenesulfonic acid in support of the assigned structure. In a similar manner,

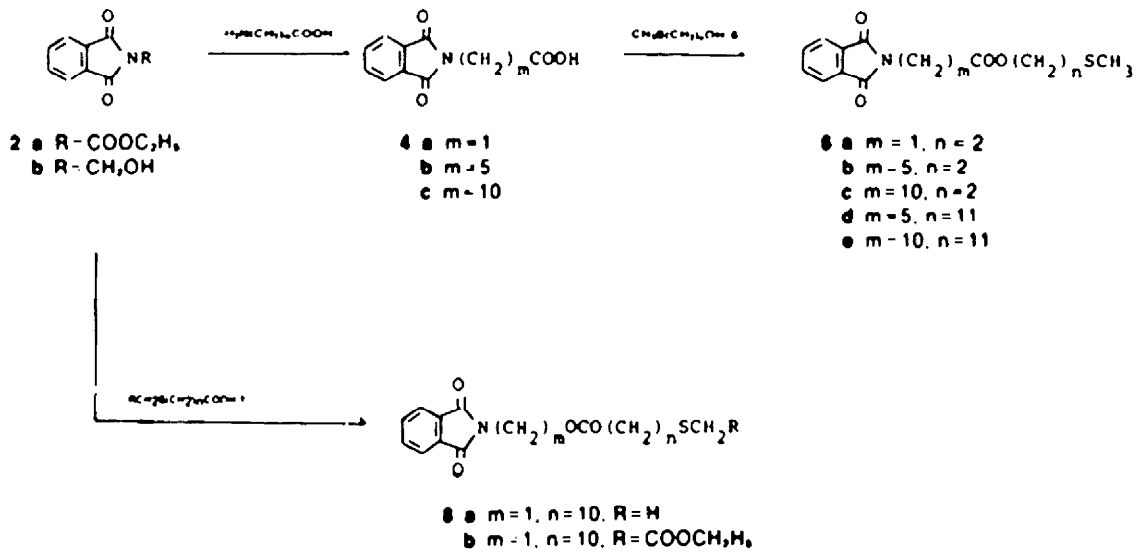


Chart 2

Table 1 Photoproducts from the substrates (6, 8)

	Substrates			Conditions			Photoproducts[b]					
	6 m	8 n	R	Weight (g) [mmol]	Conc. (mM)	Time (min)	9(12) (%)	Ring size	mp (°C)	10(13) (%)	Ring size	mp (°C)
6a	1	2	-	0.5[1.8]	6.1	34[a]	80	9	187-189*	-		
6b	5	2	-	0.7[2.1]	7.0	90[a]	36	13	171-172	3	11	166-167*
8a	1	10	H	2.1[5.4]	4.2	60	(45)	17	126-128	(7)	15	141-142
8b	1	10	COOEt	2.5[5.4]	4.2	30	(58)	17	t:121-123 c:111-112	-		
6c	10	2	-	2.5[6.2]	4.8	110	35	18	109-111	5	16	168-169
6d	5	11	-	2.0[4.3]	3.3	70	34	22	oil	3	20	158-159
6e	10	11	-	2.0[3.8]	2.9	70	48	27	125-127	10	25	143-145

(a) A 200 W high pressure mercury lamp were used for the irradiation
(b) The following abbreviations are used, t = trans, c = cis
(*) Decomposed

irradiation of **6b** afforded a mixture of the cyclized compounds, which was separated by silica gel column chromatography into **9b** and **10b**. The NMR spectrum of **9b** had a similar pattern to that described above, while that of the minor product **10b**, in which S-methylene group is involved, showed the peaks of a S-Me group at δ 2.10 and an OH group at δ 6.40 as singlet, respectively. The IR of **10b** showed signals of an OH and CO groups at ν 3260 (OH), 1730 and 1670 (CO's) cm^{-1}, respectively. From the substrates **8a** and **8b**, the azathiacyclols (**12a** and **12b**) of 17-membered ring were obtained, the former being accompanied by a minor product (**13a**). Compound **8b** afforded a mixture of the azathiacyclols **12b**, which was separated by column chromatography into the *cis* and the *trans* isomers, apparently arising from the configuration of the ethoxycarbonyl group with respect to the OH group. The assignment was made based on the NMR spectra. The Me part of the ethoxycarbonyl function in **12b** appeared as triplet peaks at δ 1.24 and 0.95, for the *cis* and *trans* isomers, respectively. The signal in the *trans* isomer shifted to a higher field than that of the corresponding *cis* isomer, due to the shielding effect of the phthalimide ring. The both isomers were converted into the same dehydrated compound **14b** (R=COOEt)

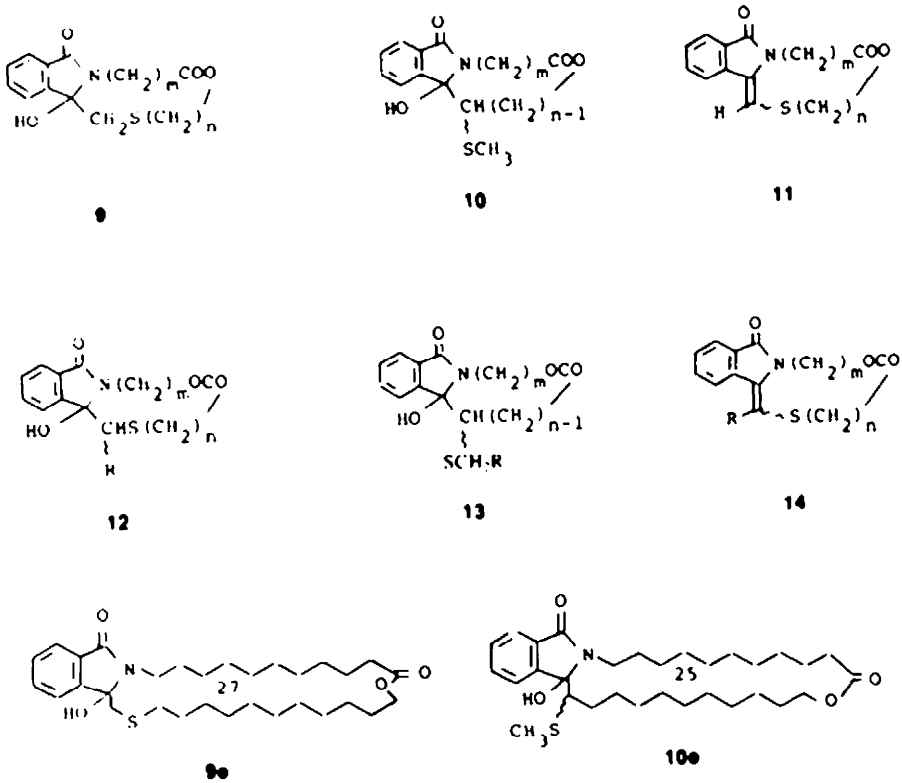


Chart 3

through manipulation with thionyl chloride–pyridine in moderate yields. The structure and stereochemistry of the azathiacyclol **12b**-*trans* were finally established by X-ray crystallographic analysis. The structure was solved by the direct method using MULTAN and was refined by the block-diagonal least-squares procedure. The final R value was 0.077 assuming anisotropic thermal parameters for the non H atoms and isotropic ones for the H atoms. A stereoscopic view of the 17-membered azathiacyclol **12b**-*trans* is illustrated in Fig. 1. During the course of our

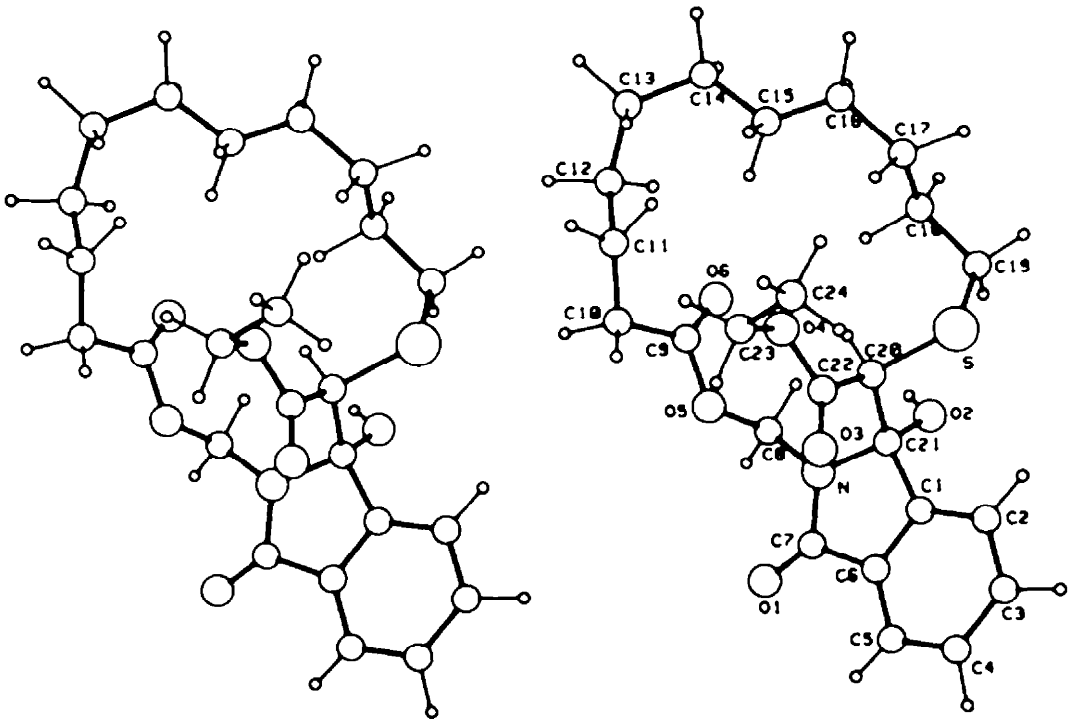


Fig. 1. Stereoscopic view of the azathiacyclol (**12b**-*trans*)

systematic photochemical macrocyclic syntheses, this is the first example of the X-ray analysis, in confirmation of the structural assignment.

Likewise, substrates **6c**, **6d** afforded the macrocycles **9c** and **9d**, with minor products **10c** and **10d**, respectively. Substrate **6e** afforded a mixture of the expected cyclols, which was separated by silica gel column chromatography into **9e** of a 27-membered ring and a minor product **10e** of a 25-membered ring. The stereoconfiguration of the above minor products **10** (**13**) is yet undetermined, but they were one of two possible isomers, respectively. The NMR and the IR data of **9e** were in support of the cyclic structure (Experimental). The molecular weight values determined by the vapor-pressure method[12] and the mass spectrometry (MS) were 532 and 531, respectively, both in agreement with the monomeric value (531).

Thus the expected macrocyclic products were obtained as a result of C–C bond formation between the imide CO group and predominantly the S-Me group through an extensive Norrish type II process.[1,7] Some minor products, in which the S-methylene group is involved, were isolated mostly in less than 10% yields. It is remarkable that H is abstracted preferentially from the Me, the less substituted C, despite the lower C–H bond strength of the methylene, which might be important if the process involves a direct abstraction of H. Such preferences have been observed in all the examples of our remote photocyclization both with ω-S-methyl-[1,7-9] and ω-N-methyl-[13] phthalimide derivatives. It has been known that photoreduction of benzophenone by,[14] and an anodic oxidation[15] of N,N-dimethylbenzylamine, both proceed by way of a cation radical intermediate leading to a similar preference for the attack on the N-Me carbon. All the above results suggest that these H transfer processes may be explained in terms of the radical cation mechanism involving the sulfide (Chart 4). Although the detailed mechanism of this remote photocyclization remains for further study, tentatively this reaction may be rationalized by rapid electron transfer followed by proton transfer from the radical-cation of methylthio group with favorable entropy factors by virtue of charge-transfer complex formation in the excited state (Chart 4).[1,7] The largest ring size obtained in the present study was a 27-membered ring **9e** derived from **6e**. To estimate the efficiency of this remote reaction, the quantum yield was measured. The quantum yield for the formation of **9e** from **6e** in acetonitrile was 0.013 ± 0.003.[7b]

In view of the methodology of the photochemical macrocyclic syntheses, it is important that the substrates (**6**, **8**) having a functional group such as the ester bond undergo smooth selective remote photocyclization at the thiomethyl group without cyclization into the chain interior. Usually in the Norrish type II photocyclization of long-chain substrates, a mixture of various products are obtained following the statistical distribution along with the chain methylenes.[4c,d] Of all macrolide-forming reactions, the lactonization of long open-chain hydroxy acids is the most general method.[16] In the present synthesis, open, long chain substrates with ester linkages are cyclized by C–C bond formation. This pair system may provide a versatile photochemical unit for the synthesis of various macrocycle analogs.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were taken on a Hitachi IR-215 (Nujol). UV spectra on a Hitachi 323. Mass (MS) spectra on a Hitachi RMS-4. NMR spectra on a JEOL MH60 ($CDCl_3$, $(Me)_4Si$ as an internal standard; the chemical shifts are expressed in δ (ppm), coupling constants (J) are given in Hz), unless otherwise specified.

11-*Methylthioundecanol* (**5**; n = 11)

A mixture of 11-bromoundecanol (50 g, 199 mmol) and MeSNa (25 g, 357 mmol) in DMF (360 ml) was stirred at 60° for 7 hr. The mixture was poured into water, extracted with ether. The extracts were washed with brine and concentrated *in vacuo* to give 36.4 g (84%) of a solid, b.p. 148–151°/3 mmHg, m.p. 33–35°. (Found: C, 66.25; H, 12.11; S, 14.49. $C_{13}H_{28}OS$ requires: C, 66.01; H, 12.00; S, 14.66%.)

1,3(2H)-*Dioxo*-2H-*isoindol*-2-*undecanoic acid* (**4c**)

Compound **2a**[17] (21.9 g, 0.1 mol) was added to a stirred soln of **3** (m = 10) (20.1 g, 0.1 mol) and Na_2CO_3 (10.6 g, 0.1 mol) in H_2O (150 ml) at 25° for 1 hr. After insoluble materials were filtered off, the filtrate was acidified and the ppts were collected by suction, washed with H_2O, and dried to give 20.8 g (63%) of **4c**, colorless needles from ether, m.p. 90–91° (Found: C, 68.66; H, 7.54; N, 4.32. $C_{19}H_{25}NO_4$ requires: C, 68.86; H, 7.60; N, 4.23%.)

General procedure for the synthesis of **6** (except for **6e**). Thionyl chloride (15 ml) was added to a solution of **4**[18] (55 mmol) in DMF (0.1 ml) and $CHCl_3$ (60 ml) at 25°. After refluxing for 2 hr,

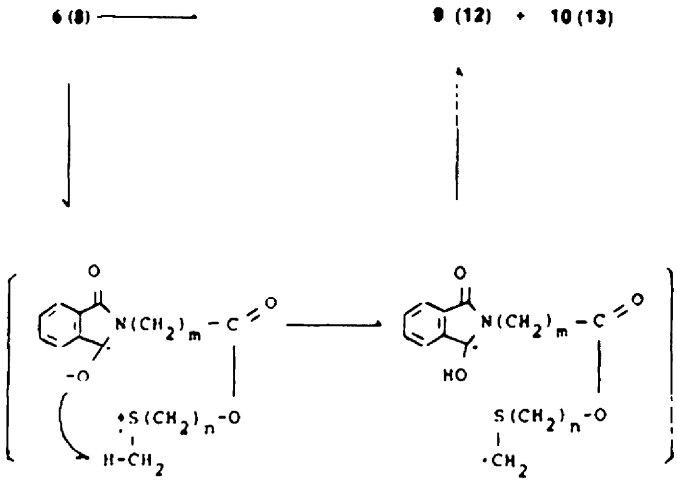


Chart 4

the solvent was evaporated to give the acid chloride,[19] which was used in the next reaction. A soln of the acid chloride (55 mmol) in CH_2Cl_2 (40 ml) was added to a stirred soln of 5 (55 mmol) and Et_3N (55 mmol) in CH_2Cl_2 (5 ml) at − 20° ~ − 40° for 30 min. After stirring for 3 hr at 25°, the mixture was poured into dil HCl and extracted with $CHCl_3$. The extracts were washed with 5% $NaHCO_3$, H_2O and concentrated *in vacuo*. The residue was purified by recrystallization or SiO_2 column chromatography.

2-(Methylthio)ethyl-1,3(2H)-dioxo-2H-isoindol-2-acetate (**6a**)

The residue was recrystallized from benzene-hexane, 13.5 g (88%) of colorless needles, m.p. 71–72°. IR: 1770, 1725 cm⁻¹. MS *m/e*: 279 (M⁺). NMR: 2.72 (2H, t, J = 7 Hz, SCH_2), 2.12 (3H, s, SCH_3). (Found: C, 55.96; H, 4.68; N, 5.08; S, 11.06. $C_{13}H_{13}NO_4S$ requires: C, 55.91; H, 4.70; N, 5.02; S, 11.46%.)

2-(Methylthio)ethyl-1,3(2H)-dioxo-2H-isoindole-2-hexanoate (**6b**)

The residue was chromatographed (hexane–AcOEt = 4 : 1), 16.3 g (89%) of a pale yellow oil. IR(liquid): 1765, 1710 cm⁻¹. MS *m/e*: 335 (M⁺). NMR: 2.69 (2H, t, J = 6.7 Hz, SCH_2), 2.14 (3H, s, SCH_3). (Found: C, 61.01; H, 6.41; N, 4.15; S, 9.68. $C_{17}H_{21}NO_4S$ requires: C, 60.88; H, 6.31; N, 4.18; S, 9.54%.)

2-(Methylthio)ethyl-1,3(2H)-dioxo-2H-isoindol-2-undecanoate (**6c**)

The residue was chromatographed (hexane–AcOEt 4 : 1, 9.5 : 0.5), 18.0 g (80.9%) of a brownish oil. IR(liquid): 1765, 1730, 1710 cm⁻¹. MS *m/e*: 405 (M⁺). NMR: 2.71 (2H, t, J = 6.8 Hz, SCH_2), 2.15 (3H, s, SCH_3). (Found: C, 64.93; H, 7.57; N, 3.53; S, 7.77. $C_{22}H_{31}NO_4S$ requires: C, 65.16; H, 7.71; N, 3.45; S, 7.89%.)

11-(Methylthio)undecyl-1,3(2H)-dioxo-2H-isoindole-2-hexanote (**6d**)

The residue was recrystallized (isopropyl-ether–hexane) after chromatography (benzene–AcOEt = 9.5 : 0.5), 5.9 g (23.2%) of colorless prisms, m.p. 48–49°. IR: 1770, 1735, 1695 cm⁻¹. MS *m/e*: 461 (M⁺). NMR: 2.68–2.19 (2H, s, SCH_2), 2.08 (3H, s, SCH_3). (Found: C, 67.88; H, 8.37; N, 3.13; S, 6.85. $C_{26}H_{39}NO_4S$ requires: C, 67.65; H, 8.52; N, 3.30; S, 6.93%.)

11-(Methylthio)undecyl-1,3(2H)-dioxo-2H-isoindol-2-undecanoate (**6e**)

A suspension of **4c** (6.62 g, 20 mmol), **5** (n = 11) (4.36 g, 20 mmol), 1-methyl-2-chloropyridinum iodide[20] (6.13 g, 24 mmol) and Et_3N (4.85 g, 48 mmol) in CH_2Cl_2 (40 ml) was refluxed under an argon atmosphere for 7 hr. After removal of the solvent, the residue was chromatographed on SiO_2 (hexane–AcOEt = 9 : 1) to give 7.61 g (71.6%) of **6e**, colorless crystals from AcOEt–hexane, m.p. 63–64°. IR: 1760, 1725, 1715, 1690 cm⁻¹. UV (MeOH): 293 nm (ε = 3620). MS *m/e*: 531 (M⁺). NMR: 2.56–2.16 (2H, m, SCH_2), 2.08 (3H, s, SCH_3). (Found: C, 70.47; H, 9.14; N, 2.64; S, 5.94. $C_{31}H_{49}NO_4S$ requires: C, 70.02; H, 9.29; N, 2.63; S, 6.02%.)

1,3(2H)-Dioxo-2H-isoindol-2-ylmethyl-11-(methylthio)-undecanoate (**8a**)

Oxalyl chloride (4.64 g, 45 mmol) was added to a stirred soln of 7 (R=H, n = 10)[21] (6.96 g, 30 mmol) in ether (30 ml) at 0°. The soln was stirred at 25° for 90 min and concentrated to give 7.75 g of the acid chloride, which was processed with **2b** (5.31 g, 30 mmol) and Et_3N (3.03 g, 30 mol) in CH_2Cl_2 (60 ml), in a manner similar to that of **6**. The residue was chromatographed on SiO_2 (hexane–AcOEt = 4 : 1) to give 5.7 g (49%) of **8a**, colorless needles from ether–hexane, m.p. 73–74°. IR: 1780, 1740, 1710 cm⁻¹. UV ($CHCl_3$): 303 (sh, ε = 2090), 296 nm (2340). MS *m/e*: 391 (M⁺). NMR: 2.62–2.18 (2H, m, SCH_2), 2.08 (3H, s, SCH_3). (Found: C, 64.63; H, 7.47; N, 3.60; S, 7.99. $C_{21}H_{29}NO_4S$ requires: C, 64.43; H, 7.47; N, 3.58; S, 8.17%.)

1,3(2H)-Dioxo-2H-isoindol-2-ylmethyl-11-[ethoxycarbonyl)-methylthio]undecanoate (**8b**)

A suspension of 11-bromoundecanoic acid (26.62 g, 0.1 mol), ethyl-2-mercaptacetate (15.63 g, 0.13 mol) and K_2CO_3 (27.6 g, 0.2 mol) in DMF (200 ml) was stirred under an argon atmosphere at 25° for 24 hr. The mixture was poured into dil HCl and extracted with ether. The extracts were washed with brine, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt = 4 : 1) to give 28.3 g (93%) of 7 (R=COOEt, n = 10), which was used in the following step. A suspension of 7 (R=COOEt, n = 10) (13.6 g, 44.8 mmol), **2b** (8.72 g, 49.3 mmol), 1-methyl-2-chloro-pyridinum iodide (13.8 g, 53.8 mmol) and Et_3N (10.9 g, 0.108 mol) in CH_2Cl_2 (90 ml) was refluxed under an argon atmosphere for 2 hr. After removal of the solvent, the residue was purified by SiO_2 chromatography (hexane–AcOEt = 4 : 1) to give 11.6 g (77%) of **8b**, colorless needles from ether–hexane, m.p. 37.5–38.5°. IR: 1775, 1730 cm⁻¹. MS *m/e*: 463 (M⁺). NMR: 3.20 (2H, s, SCH_2), 2.75–2.03 (2H, m, SCH_2). (Found: C, 62.19; H, 7.23; N, 3.11; S, 6.88. $C_{24}H_{33}NO_6S$ requires: C, 62.19; H, 7.18; N, 3.02; S, 6.91%.)

General procedure for the irradiation. A soln of **6** or **8** [0.5–2.5 g (1.8–7.8 mmol)] in acetone (2.9–7.0 mM) was irradiated with a 400 W high pressure mercury lamp at 10–20° for 30–110 min in a stream of argon. After removal of the solvent in vacuo, the residue was subjected to SiO_2 chromatography, followed by recrystallization of each fraction, unless otherwise specified (Table 1).

3,4,6,7,9,13b-Hexahydro-13b-hydroxy-1H-[1,4,7]oxathiazonino[6,7-a]isoindole-6,9-dione (**9a**)

The residue was recrystallized (AcOEt) to give 408 mg (80%), colorless crystals, m.p. 187–189° (dec.). IR: 3380, 1740, 1695, 1685 cm⁻¹. MS *m/e*: 279 (M⁺). NMR ($CDCl_3$–DMSO-d_6): 7.88–7.42 (4H, m, arom. H), 6.45 (1H, s, OH), 4.82 and 3.91 (2H, ABq, J = 16 Hz, NCH_2), 4.93–4.5 (1H, m, OCH), 4.0–3.57 (1H, m, OCH), 3.56 and 2.98 (2H, ABq, J = 14.8 Hz, SCH_2), 3.2–2.67 (2H, m, SCH_2). (Found: C, 55.45; H, 4.90; N, 4.88; S, 11.04. $C_{13}H_{13}NO_4S$ requires: C, 55.91; H, 4.70; N, 5.02; S, 11.46%.)

3,4,6,7,8,9,10,11,13,17b-Decahydro-17b-hydroxy-1H-[1,4,7]-oxathiazacyclotridecino[6,7-a]isoindole-6,13-dione (**9b**) *and 1,2,4,5,6,7,8,9,11,15b-decahydro-15b-hydroxy-1-methylthio-[1,5]oxazacycloundecino[4,5-a]isoindole-4,11-dione* (**10b**)

The residue was separated by chromatography (AcOEt–hexane = 3 : 2). **9b** (more polar) was recrystallized (benzene–AcOEt) to give 253 mg (36.1%), colorless prisms, m.p. 171–172°. Molecular weight (MW): Calc 335, found 344 (in MeOH). IR: 3260, 1730, 1670 cm⁻¹. MS *m/e*: 335 (M⁺). NMR: 7.7–7.3 (4H, m, arom. H), 4.83 (1H, s, OH), 4.18 (2H, t, J = 5.4 Hz, OCH_2), 3.55 and 3.11 (2H, ABq, J = 15.6 Hz, SCH_2), 3.4–3.0 (2H, m, NCH_2), 2.74 (2H, t, J = 5 Hz, SCH_2), 2.33 (2H, m, $COCH_2$), 2.1–1.2 (6H, m, 3 × CH_2). (Found: C, 60.71; H, 6.32; N, 4.35; S, 9.43. $C_{17}H_{21}NO_4S$ requires: C, 60.88; H, 6.31; N, 4.18; S, 9.54%.)

Compound **10b** (less polar) was recrystallized (EtOH) to give 66 mg (9.4%), colorless prisms, m.p. 166–167° (dec.). MW: Calc 335, found 333 (in MeOH). IR: 3260, 1730, 1670 cm⁻¹. MS *m/e*: 335 (M⁺). NMR: 7.8–7.4 (4H, m, arom. H), 6.40 (1H, s, OH), 4.81 (1H, ABXq, J = 11.8, 2.0 Hz, OCH), 3.59 (2H, m, NCH_2), 3.42 (1H, ABXq, J = 5.5, 2.0 Hz, SCH), 3.30 (1H, ABXq, J = 11.8, 5.5 Hz, OCH), 2.31 (2H, m, $COCH_2$), 2.01 (3H, s, SCH_3), 2.0–1.0 (6H, m, 3 × CH_2). (Found: C, 60.85; H, 6.44; N, 4.18; S, 9.42. $C_{17}H_{21}NO_4S$ requires: C, 60.88; H, 6.31; N, 4.18; S, 9.54.)

3,4,7,8,9,10,11,12,13,14,15,16,18,22b-Tetradecahydro-22b-hydroxy-1H,6H-[1,4,7]oxathiazacyclooctadecino[6,7-a]isoindole-6,18-dione (**9c**) *and 1,2,5,6,7,8,9,10,11,12,13,14,16,20b-tetradecahydro-20b-hydroxy-1-methylthio-4H-[1,5]oxazacyclohexadecino[4,5-a]isoindole-4,16-dione* (**10c**)

The residue was separated by chromatography (hexane–AcOEt = 3 : 2). **9c** (more polar) was recrystallized (isopropyl ether) to give 865 mg (34.6%), colorless prisms, m.p. 109–111°. MW: Calc 405, found 389 (in MeOH). IR: 3270, 1725, 1670 cm⁻¹. MS *m/e*: 405 (M⁺). NMR: 7.66–7.26 (4H, m, arom. H), 4.88 (1H, s, OH), 4.38–3.78 (2H, m, OCH_2), 3.12 (2H, s, SCH_2), 3.06 (2H, m, NCH_2), 2.54 (2H, q, J = 12.6 Hz, SCH_2), 2.28 (2H, t, J = 7 Hz, $COCH_2$), 1.8–1.0 (16H, m, 8 × CH_2). (Found: C, 64.82; H, 7.71; N, 3.31; S, 7.81. $C_{22}H_{31}NO_4S$ requires: C, 65.16; H, 7.71; N, 3.45; S, 7.89%.)

Compound **10e** (less polar) was recrystallized (AcOEt–hexane) to give 131 mg (5.2%), colorless needles, m.p. 168–169°. MW: Calc 405; found 404 (in MeOH). IR: 3220, 1720, 1665 cm^{-1}. MS *m/e*: 405 (M^+). NMR: 7.4 (4H, m, arom. H), 5.14 and 4.34 (2H, each ABXq, J = 12, 6 Hz, OCH_2), 4.59 (1H, s, OH), 3.31 (2H, m, NCH_2), 3.0 (1H, m, SCH), 2.39 (2H, t, J = 6 Hz, $COCH_2$), 1.86 (3H, s, SCH_3), 1.8–1.0 (16H, m, 8 × CH_2). (Found: C, 65.75; H, 7.71; N, 3.32; S, 7.55. $C_{22}H_{31}NO_4S$ requires: C, 65.16; H, 7.71; N, 3.45; S, 7.89%.)

4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 22, 26b-*Octadecahydro* - 26b - *hydroxy* - 1H,3H - [1,11,8]*oxathiazacyclodocosino*[9,8 - a]*isoindole* - 15,22 - *dione* (**9d**) *and* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 20, 24b - *octadecahydro* - 24b - *hydroxy* - 1 - *methylthio*[1,8]*oxazacycloeicosino*[9,8 - a]*isoindole* - 13, 20 - *dione* (**10d**)

The residue was separated by chromatography (hexane–AcOEt = 3:2). **9d** (more polar) was obtained 677 mg (33.9%), a pale yellow oil. MW: Calc 461, found 414 (in MeOH). IR ($CHCl_3$): 3330, 1730–1695 cm^{-1}. MS *m/e*: 461 (M^+). NMR: 7.6–7.3 (4H, m, arom. H), 4.76 (1H, s, OH), 4.02 (2H, m, OCH_2), 3.2 and 3.04 (2H, ABq, J = 14 Hz, SCH_2), 3.48–2.76 (2H, m, NCH_2), 2.34 and 2.27 (4H, d.t, J = 7 Hz, SCH_2, $COCH_2$), 1.8–1.1 (24H, m, 12 × CH_2). (Found: C, 67.19; H, 8.59; N, 2.56; S, 6.72. $C_{26}H_{39}NO_4S$ requires: C, 67.65; H, 8.52; N, 3.03; S, 6.93%.)

Compound **10d** (less polar) was recrystallized (AcOEt–hexane) to give 51 mg (2.6%), colorless prisms, m.p. 158–159°. MW: Calc 461, found 478 (in MeOH). IR: 3200, 1725, 1675 cm^{-1}. MS *m/e*: 461 (M^+). NMR: 8.0–7.3 (4H, m, arom. H), 4.11 (1H, s, OH), 4.11 (2H, m, OCH_2), 3.24 (2H, m, NCH_2), 2.90 (1H, m, SCH), 2.45 (3H, s, SCH_3), 2.34 (2H, t, J = 7 Hz), 1.30 (24H, m, 12 × CH_2). (Found: C, 67.24; H, 8.47; N, 2.78; S, 6.61. $C_{26}H_{39}NO_4S$ requires: C, 67.65; H, 8.52; N, 3.03; S, 6.93%.)

4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 31b, *Docosahydro* - 31b - *hydroxy* - 1H,3H,15H - [1,13,16]*oxathiazacycloheptacosino* [15,16 - a]*isoindole* - 15,27 - *dione* (**9e**) *and* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 29b - *docosahydro* - 29b - *hydroxy* - 1 - *methylthio* - 1H,13H - [1,13]*oxazacyclopentacosino*[14,13 - a]*isoindole* - 13,25 - *dione* (**10e**)

The residue was separated by chromatography (hexane–AcOEt = 7:3). **9e** (more polar) was recrystallized ($CHCl_3$–hexane) to give 962 mg (48%), colorless needles, m.p. 125–127°. MW: Calc 531, found 532 (in MeOH). IR: 3200, 1735, 1680, 1665 cm^{-1}. MS *m/e*: 531 (M^+). NMR: 7.63–7.28 (4H, m, arom. H), 4.57 (1H, s, OH), 4.05 (2H, t, J = 6 Hz, OCH_2), 3.4–2.77 (2H, m, NCH_2), 3.23 and 3.0 (2H, ABq, J = 14 Hz, SCH_2), 2.36 (2H, m, $COCH_2$), 2.28 (2H, t, J = 7 Hz, SCH_2), 1.8–1.0 (34H, m, 17 × CH_2). (Found: C, 70.11; H, 9.14; N, 2.51; S, 5.99. $C_{31}H_{49}NO_4S$ requires: C, 70.02; H, 9.29; N, 2.63; S, 6.02%.)

Compound **10e** (less polar) was recrystallized ($CHCl_3$–hexane) to give 196 mg (9.8%), colorless prisms, m.p. 143–145°. MW: Calc 531, found 529 (in MeOH). IR: 3260, 1730, 1670 cm^{-1}. MS *m/e*: 531 (M^+). NMR: 8.0–7.28 (4H, m, arom. H), 4.29 (1H, s, OH), 4.0 (2H, m, OCH_2), 3.19 (2H, m, NCH_2), 2.9 (1H, m, SCH), 2.4 (3H, s, SCH_3), 2.3 (2H, m, $COCH_2$), 1.9–0.8 (34H, m, 17 × CH_2). (Found: C, 69.71; H, 8.97; N, 2.50; S, 5.95. $C_{31}H_{49}NO_4S$ requires: C, 70.02; H, 9.29; N, 2.63; S, 6.02%.)

4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 17, 21b - *Dodecahydro* - 21b - *hydroxy* - 1H, 3H,15H - [1,6,3]*oxathiazacycloheptadecino*[4,3 - a] - *isoindole* - 13,17 - *dione* (**12a**) *and* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 15, 19b - *dodecahydro* - 19b - *hydroxy* - 1 - *methylthio* - 1H,13H - [1,3]*oxazacyclopentadecino*[4,3 - a]*isoindole* - 11,15 - *dione* (**13a**)

The residue was separated by chromatography (hexane–AcOEt = 3:1). **12a** (more polar) was recrystallized (AcOEt) to give 0.95 g (45%), colorless needles, m.p. 126–128°. MW: Calc 391, found 387 (in $CHCl_3$). IR: 3280, 1745, 1685 cm^{-1}. UV (MeOH): 234 (ε = 7720), 228 (10100), 220 nm (10260). MS *m/e*: 391 (M^+). NMR: 8.1–7.45 (4H, m, arom. H), 5.31 (2H, s, NCH_2), 4.43 (1H, br s, OH), 3.27 and 2.92 (2H, ABq, J = 14 Hz, SCH_2), 2.7–2.1 (4H, m, SCH_2, $COCH_2$), 2.0–1.0 (16H, m, 8 × CH_2). (Found: C, 64.38; H, 7.37; N, 3.56; S, 8.12. $C_{21}H_{29}NO_4S$ requires: C, 64.43; H, 7.47; N, 3.58; S, 8.17%.) **13a** (less polar) was

Compound **13a** (less polar) was recrystallized (ether–hexane) to give 0.15 g (7.1%), colorless needles, m.p. 141–142°. MW: Calc 391, found 390 (in $CHCl_3$). IR: 3300, 1735, 1690 cm^{-1}. UV (MeOH): 235 (ε = 7130), 229 (8860), 222 nm (8780). MS *m/e*: 391 (M^+). NMR: 8.1–7.45 (4H, m, arom. H), 5.53 and 5.24 (2H, ABq, J = 11.5 Hz, NCH_2), 4.25 (1H, br m, OH), 3.0 (1H, d, SCH), 2.55–2.15 (2H, m, $COCH_2$), 2.32 (3H, s, SCH_3), 2.0–1.0 (16H, m, 8 × CH_2). (Found: C, 64.27; H, 7.41; N, 3.54; S, 8.20. $C_{21}H_{29}NO_4S$ requires: C, 64.43; H, 7.47; N, 3.58; S, 8.17%.)

1 - *Ethoxycarbonyl* - 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 17, 21b - *dodecahydro* - 21b - *hydroxy* - 1H,3H,15H - [1,6,3]*oxathiazacycloheptadecino*[4,3 - a] *isoindole* - 13,17 - *dione* (**12b**) (*trans and cis*)

The residue was separated by chromatography (hexane–AcOEt = 2:1). **12b** (*cis*; more polar) was recrystallized (ether–hexane) to give 0.4 g (16%), colorless prisms, m.p. 111–112°. MW: Calc 463; found 459 (in MeOH). IR: 3250, 1750, 1730, 1700 cm^{-1}. MS *m/e*: 463 (M^+). NMR: 8.06–7.24 (4H, m, aroen. H), 5.77 and 5.3 (2H, ABq, J = 11.5 Hz, NCH_2), 4.94 (1H, m, OH), 4.1 (2H, q, J = 7.2 Hz, OCH_2), 4.0 (1H, s, CH), 3.0–2.0 (4H, m, $COCH_2$, SCH_2), 1.24 (3H, t, J = 7 Hz, CH_3), 2.0–1.0 (16H, m, 8 × CH_2). (Found: C, 62.21; H, 7.06; N, 3.01; S, 6.90. $C_{24}H_{33}NO_6S$ requires: C, 62.19; H, 7.18; N, 3.02; S, 6.91%.) **12b** (*trans*, less polar) was recrystallized ($CHCl_3$–hexane) to give 1.05 g (42%), colorless needles, m.p. 121–123°. MW: Calc 463; found 465 (in MeOH). IR: 3280, 1740, 1690 cm^{-1}. MS *m/e*: 463 (M^+), 417, 160. NMR: 8.03–7.44 (4H, m, arom. H), 5.52 (2H, s, NCH_2), 4.21 (1H, s, CH), 4.08 (1H, s, OH), 3.98 (2H, m, OCH_2), 3.0–2.1 (4H, m, $COCH_2$, SCH_2), 1.38 (16H, m, 8 × CH_2), 0.95 (3H, t, J = 6.9 Hz, CH_3). [Found: C, 62.16; H, 7.18; N, 2.96; S, 6.96. $C_{24}H_{33}NO_6S$ requires: C, 62.19; H, 7.18; N, 3.02; S, 6.91%.]

3,4,6,7-*Tetrahydro*-9H - [1,4,7]*oxathiazonino*[6,7 - a] *isoindole* - 6,9 - *dione* (**11a**)

Method A. A soln of **9a** (500 mg, 1.79 mmol) and *p*-toluensulfonic acid (100 mg) in CH_2Cl_2 (50 ml) was refluxed for 1 hr. After removal of the solvent, the residue was chromotographed on SiO_2 (benzene–AcOEt = 9.5:0.5) to give 200 mg (40%) of **11a**, colorless prisms from $CHCl_3$–ether, m.p. 186–188°. IR: 1735, 1710 cm^{-1}. MS *m/e*: 261 (M^+). NMR: 8.0–7.4 (4H, m, arom. H), 6.42 (1H, s, olefinic H), 5.6–4.0 (4H, m, NCH_2, OCH_2), 2.95 (2H, t, J = 6.3 Hz, SCH_2). (Found: C, 59.46; H, 4.34; N, 5.23; S, 12.09. $C_{13}H_{11}NO_3S$ requires: C, 59.77; H, 4.24; N, 5.36; S, 12.25%.)

1 - (*Ethoxycarbonyl*) - 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 - *decahydro* - 3H,15H,13H - *oxathiazacycloheptadecino* [4,3 - a]*isoindole* - 13,17 - *dione* (**14b**)

Method B. Thionyl chloride (51.4 mg, 0.43 mmol) was added to a stirred soln of **12b**-*trans* (100 mg, 0.22 mmol) in pyridine (1 ml) at −30°. The soln was stirred at −30° for 2 hr and then at 25° for 3 hr. The mixture was poured into H_2O and extracted with CH_2Cl_2. The extracts were washed with 10% HCl, dried, and concentrated *in vacuo*. The residue was purified by SiO_2 preparative TLC (hexane–AcOEt = 2:1) to give 61 mg (64%) of a yellow oil. IR(hquid): 1735, 1610, 1585 cm^{-1}. MS *m/e*: 446 (M^+ + 1), 455 (M^+). NMR: 9.16–8.9 (1H, m, arom. H), 8.0–7.4 (3H, m, arom. H), 6.75 and 5.47 (2H, ABq, J = 11.4 Hz, NCH_2), 4.36 (2H, q, J = 7.4 Hz, OCH_2), 3.0–2.0 (4H, m, $COCH_2$, SCH_2), 2.0–1.0 (19H, m, 8 × CH_2, CH_3). (Found: C, 64.55; H, 7.00; N, 3.16; S, 7.02. $C_{24}H_{31}NO_5S$ requires: C, 64.70; H, 7.01; N, 3.14; S, 7.18%.)

Dehydration of **12b**-*cis* was processed in the same manner as described for **12b**-*trans* to give 52% of **14b**, which was identical with the above compound (**14b**)

3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 - *Dodecahydro* - 18H - [1,4,7] - *oxathiazacyclooctadecino*[6,7 - a]*isoindole* - 6,18 - *dione* (**11c**)

According to Method B, **11c** was obtained as a colorless oil after SiO_2 chromatography (hexane–AcOEt = 9:1) in 40% yield. IR($CHCl_3$): 1730, 1690, 1610 cm^{-1}. MS *m/e*: 387 (M^+). NMR: 8.31–7.46 (4H, m, arom. H), 6.05 (1H, s, olefinic H), 4.33 (2H, t, J = 7 Hz, SCH_2), 3.81 (2H, t, J = 6.6 Hz, OCH_2), 3.60 (2H, t, J = 7 Hz, NCH_2), 2.37 (2H, t, J = 5 Hz, $COCH_2$), 1.31 (16H, m,

8 × CH_3). (Found: C, 68.27; H, 7.65; N, 3.67; S, 8.10. $C_{22}H_{25}NO_3S$ requires: C, 68.19; H, 7.54; N, 3.62; S, 8.26%.)

X-ray crystallographic analysis

The crystal data for **12b-trans** which is recrystallized from ether as colorless plates; $C_{24}H_{21}NO_4S$ (MW 463.60) are as follows; triclinic, space group: P_1, $A = 11.707(1)$, $b = 13.528(2)$, $c = 8.439(1)$ Å, $\alpha = 103.377(6)$, $\beta = 86.796(7)$, $\gamma = 112.283(5)°$, $V = 1202.4$ Å^3, $D_{calc} = 1.280$ g/cm^3, $Z = 2$. The intensity data were collected on a Rigaku automatic four-circle diffractometer (AFC-3) using CuKα radiation monochromated by means of a graphite plate; 4081 independent reflections with 2θ less than 130° were measured of which 2823 were considered observed, having $|Fo| \geq 3\sigma(|Fo|)$. The intensities were corrected for the Lorentz and polarization factors but no absorption correction was applied.

Quantum yields

Acetonitrile solns of a sample of **6e** (10 mM) in Pyrex tubes were degassed by five freeze-pump-thaw cycles and sealed *in vacuo* at $\leq 10^{-3}$ Torr. Quantum yields were measured relative to 0.012 M potassium ferrioxalate actinometer[22] on parallel irradiation of samples of identical volumes (5 ml). Irradiations were performed on a merry-go-round apparatus with a Eikosha 500 W high pressure mercury lamp contained in a water-cooled, quartz immersion well. A chemical filter of 1.4 mM potassium chromate in 0.1% Na_2CO_3aq[23] was used to isolate the 313 nm line. After the irradiation, the products were isolated by silica gel preparative TLC (Merck pre-coated PLC 60F-254, $CHCl_3$–MeOH = 20:1) and product formations were determined by measurement of optical densities in EtOH at 250 nm. Quantum yield of the formation of **9e** from **6e** was 0.013 ± 0.003.

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REFERENCES

[1a]Photochemistry of the Phthalimide System. 31. Part 30: M. Wada, H. Nakai, Y. Sato, Y. Hatanaka and Y. Kanaoka, *Chem. Pharm. Bull.*, in press; [b]Photoinduced Reactions 64. Part 63: see Ref. 1a.

[2a]P. Lauger, *Science* **178**, 24 (1972); [b]B. C. Pressman, *Ann. Rev. Biochem.* **45**, 501 (1976); [c]Y. Ovchinnikov, *Membrane-Active Complexmones*, p. 1. Elsevier, Amsterdam (1974).

[3a]D. J. Cram and J. M. Cram, *Acc. Chem. Res.* **11**, 8 (1978); [b]J. M. Lehn, *Ibid.* **11**, 49 (1978); [c]H. Dugas and C. Penny *Bioorganic Chemistry* (Edited by R. Frost), p. 255. Springer-Verlag, New York (1981).

[4a]J. S. Bradshow and P. E. Stott, *Tetrahedron* **36**, 461 (1980); [b]G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, **14**, 95 (1981); [c]M. A. Winnik, *Chem. Rev.* **81**, 491 (1981); [d]R. Breslow, *Chem. Soc. Rev.* **1**, 553 (1972).

[5]Y. Kanaoka, *Acc. Chem. Res.* **11**, 407 (1978).

[6a]Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi, Y. Migita and Y. Kanaoka, *Tetrahedron Letters* 1973, 4565. [b]Y. Sato, H. Nakai, T. Mizoguchi, M. Kawanishi, Y. Hatanaka and Y. Kanaoka, *Chem. Pharm. Bull.* **30**, 1263 (1982).

[7a]Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka and Y. Kanaoka, *J. Am. Chem. Soc.* **98**, 2349 (1976); [b]In preliminary studies with N-[(ω-methylthio)hexyl]phthalimide[7a], the quantum yield of the cyclization was 0.05 (in CH_3CN; 313 nm). Relative efficiencies of **6e** were in same order.

[8]Y. Sato, H. Nakai, T. Mizoguchi and Y. Kanaoka, *Tetrahedron Letters*, 1976, 1889.

[9]M. Wada, H. Nakai, Y. Sato and Y. Kanaoka, *Tetrahedron Letters* **23**, 3077 (1982).

[10]M. Kozumi, *Organic Photochemistry* (Edited by T. Matsuura and H. Nozaki), Nankodo Co., Tokyo, Kagakuno-Ryoiki Zokan **93**, 1 (1970) (in Japanese).

[11]M. Wada, H. Nakai, K. Aoe, K. Kotera, Y. Sato and Y. Kanaoka, *Chem. Pharm. Bull.* **30**, 2275 (1982).

[12]Hitachi-Perkin molecular weight measuring apparatus Model 115, in MeOH or $CHCl_3$.

[13a]M. Machida, H. Takechi and Y. Kanaoka, *Heterocycles* **7**, 273 (1977). [b]*Idem, Chem. Pharm. Bull.* **30**, 1579 (1982).

[14]S. G. Cohen and N. M. Stein, *J. Am. Chem. Soc.* **93**, 6542 (1971).

[15]J. E. Barry, M. Finbelstein, E. A. Mayeda and S. D. Ross, *J. Org. Chem.* **39**, 2695 (1974).

[16]K. C. Nicolaou, *Tetrahedron* **33**, 683 (1977).

[17a]G. H. L. Nefkens, G. I. Tesser and R. J. F. Nivard, *Rec. Trav. Chim.* **79**, 688 (1960); [b]G. H. L. Nefkens, *Nature* **185**, 309 (1960).

[18a]J. H. Billmann and W. F. Hartung, *J. Am. Chem. Soc.* **70**, 1473 (1949); [b]S. Gabriel and J. Colman, *Chem. Ber.* **41**, 2015 (1908); [c]K. A. Bottcher, *Chem. Ber.* **46**, 3158 (1913).

[19]J. C. Sheehan and V. S. Frank, *J. Am. Chem. Soc.* **71**, 1856 (1949).

[20a]T. Mukaiyama, M. Usui, E. Shimada and K. Saigo, *Chem. Lett.* 1975, 1045; [b]K. Saito, M. Usui, K. Kikuchi, E. Shimada and T. Mukaiyama, *Bull. Chem. Soc. (Japan)* **50**, 1863 (1977).

[21]I. Rapoport, A. Smith and M. S. Newman, *J. Am. Chem. Soc.* **69**, 693 (1947).

[22]C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc. (London)* **A235**, 518 (1956).

[23]S. L. Murov, *Handbook of Photochemistry*, p. 99. Marcell Dekker, New York (1973).